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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/477,983	06/07/95	RUBIN J	40399/321/NI

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EXAMINER	
SAOUD, C	
ART UNIT	**PAPER NUMBER**
1646	23
DATE MAILED:	04/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/477,983	RUBIN et al.
Examiner	**Group Art Unit**
SAOUD	1646

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 8/28/98, 11/20/98, 1/29/99.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 44-88 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 44-88 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 17, 20

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

DETAILED ACTION

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 28 August 1998 has been entered.

Response to Amendment

2. Claims 13-14, 23-24, 29, 36-37, 39 and 40-43 have been canceled and claims 44-77 have been added as requested in the amendment of paper #21, filed 2 November 1998. Claims 78-88 have been added in the amendment of paper #22, filed 29 January 1999. Claims 44-88 are pending in the instant application.

Paper #21 also included an amendment to the specification. However, this amendment could not be entered because there is no page 103. Applicant should incorporate this amendment into the substitute specification which is required in response to this Office action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn. Applicant should note that it appears that no

arguments were filed in the instant application in response to the last Office action or accompanying the amendments of papers #21-22.

Specification

5. The previous Office actions in the instant application have requested a substitute specification. Any response to the instant Office action that does not include a properly filed substitute specification will be considered non-responsive.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 44-88 are provisionally rejected under the judicially created doctrine of double patenting over claims 63-76 of copending Application No. 08/455,620. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: KGF polypeptides related to Figure 7 of the instant application. The wording of the claims in the two applications is different, however, the subject matter of keratinocyte growth factor is the same.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

8. Claims 45-46, 48-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for KGF of Figure 7 (with or without the signal peptide of amino acids 1-31) and KGF polypeptides which are truncated within the region of amino acids 32-

78, does not reasonably provide enablement for any KGF polypeptide which lacks the amino acid sequence of Figure 7 with the exceptions noted. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification teaches a keratinocyte growth factor (KGF) of 194 amino acids in length and DNA encoding said KGF. The specification also teaches that the first 31 amino acids are a signal sequence that is cleaved in the mature protein and that amino acids 32-78 confer epithelial cell specificity to the protein.

Claims 45-46, 48-49, 81-82, and 84-85 are directed to KGF polypeptides that have various stimulatory activity on NIH/3T3 cells. However, the instant specification only provides for a single KGF molecule that has a very specific stimulatory activity on these cells. The instant specification does not teach how to obtain varying degrees of stimulatory activity because the instant specification fails to teach those portions of the disclosed protein which are necessary for this activity. The instant specification discloses a protein which has an amino acid sequence as disclosed in Figure 7. However, the instant claims encompass variants of the disclosed protein which has varying activities for BALB/MK cells relative to NIH/3T3 fibroblasts. It would require undue experimentation for one of ordinary skill in the art to determine which proteins which meet the structural limitation of the claims would also meet the functional limitations. Furthermore, the instant specification provides evidence that amino acids 32-78 (see Figure 7) are ***responsible*** for

conferring epithelial cell specificity to the protein and therefore, would be critical or essential to the practice of the invention. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Claims 58, 63, 67, and 78 require the polypeptide to comprise "a sufficient number of amino acids 32-64 of Figure 7 to confer on said polypeptide mitogenic activity on BALB/MK" cells. However, the instant specification provides support that these amino acids are not responsible for the mitogenic activity of the claims. Rather, these amino acids confer epithelial cell specificity to the polypeptide. Therefore, the claims are not enabled because no number of the recited amino acids alone would provide for the activity recited in the claims.

Claim 78 is directed to polypeptide which has a portion of the N-terminus of KGF (amino acids 32-64) and a C-terminus of amino acids 65-157 and 161-189, "having at least one conservative amino acid substitution therein". There is no upper limit on the number of substitutions that could made to these amino acids, therefore, the entire region could potentially be substituted as long as function is retained (by definition of "conservative substitution" which means to conserve function). The instant specification is not enabled for this breadth because the only protein which is exemplified in the instant application is the protein of Figure 7. This protein is a human protein and has the amino acid sequence described in Figure 7. The instant claims encompass any protein that has a portion of amino acids 32-64 of KGF and a particular activity. However, as stated previously, these amino acids alone are not sufficient to provide the function required by the claims. The instant specification has only enabled a single protein which possesses this activity. The specification has also demonstrated chimeric proteins wherein amino acids 32-

78 of KGF (see Figure 7) fused to portions of other FGF's result in proteins which have preferential mitogenic activity for BALB/MK cells relative to fibroblasts. However, this does not provide enablement for any protein other than that disclosed in Figure 7 or truncations described above because one of ordinary skill in the art would not know how to make a protein other than that described. This is because the instant specification lacks the appropriate guidance to alter the disclosed protein and obtain one with the required activity. The instant specification defines KGF as including mutants and or having and at least one or more amino acid differences. (see pages 7 and 10). However, the specification is only enabling for KGF having the amino acid sequence found in Figure 7 (or specific portions as outlined above) because it does not describe the production of any KGF ***lacking*** that sequence.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

By following the guidance presented in the instant specification and sound scientific principles, a practitioner can **not** produce a KGF lacking the disclosed amino acid sequence and predict the functional properties of that protein.

Additionally, the pending claims encompass non-naturally occurring mutants of KGF having the disclosed amino acid sequence but does not explicitly identify those amino acid residues which are critical for the biological activity of KGF (except for amino acids 32-78 which confer specificity). In the absence of guidance, a practitioner of the art of molecular biology would have to resort to a substantial amount of experimental trial and error in the form of deletional and substitutional analysis to identify those critical residues as would be needed to produce a mutant of the disclosed KGF protein (except for N-terminal truncations of amino acids 32-78). This trial and error would clearly constitute undue experimentation and, therefore, the instant specification is not enabling for the production of such mutants, which are clearly intended by the use of the KGF or KGF-like polypeptide in the claims. The standard for an enabling disclosure is not one of making and testing and the claims constitute a "wish to know". In so far as the instant claims encompass a KGF protein having a sequence other than the disclosed sequence identified above, specific case law bears on this issue: Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 18 U.S.P.Q. 2d, 1016, held that;

> "A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and describe how to obtain it. *See Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define

> it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated."

The fact pattern is directly analogous in that what is claimed are proteins that have yet to be isolated or characterized for the activity recited in the application and thereby constitutes a "wish to know" rather than a reduction to practice, absent evidence to the contrary. *In re Clarke*, 148 USPQ 665, (CCPA 1966) held that;

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189 ; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.21 270, 48 USPQ 397 . The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of a small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably large number of reductions to practice would probably be necessary.

With regard to claims 74 and 75, the instant specification is not enabled for "antibodies that selectively bind said polypeptide", because selectively binding to the exclusion of all other polypeptides would require a knowledge of the amino acid sequence of all proteins that exist, and this information is not present in the instant specification or in the art of record. This rejection is being made due to the ambiguity of the recitation of "selectively bind"; see 112/2nd rejection

below. In addition, it is not clear that the specification enables segments of the amino acid sequence of Figure 7 that would produce an antibody that would not significantly cross react with other proteins because there is so much similarity between the protein of Figure 7 and other FGF family members. Lastly, a sequence comparison of the amino acid sequence with the sequences of other proteins in a database reveals at least 50 different proteins that share stretches of at least 5 amino acids, which is sufficient to produce an antibody. Therefore, without a specific recitation of a length for the "segment", it would appear that a generic segment would not be enabled for producing an antibody that was selective, absent evidence to the contrary.

9. Claims 45-46, 48-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 58-88 refer to a polypeptide that comprises "a sufficient number of amino acids 32-64 to confer on the polypeptide said preferential mitogenic activity". However, the instant specification fails to convey this concept in the instant specification, especially in light of the fact that these amino acids do not confer mitogenic activity, but rather, cell specificity. As was indicated in the previous Office action, the specification teaches a keratinocyte growth factor (KGF) of 194 amino acids in length and DNA encoding said KGF. The specification also teaches that the first 31 amino acids are a signal sequence that is cleaved in the mature protein and that

amino acids 32-78 confer epithelial cell specificity to the protein. There is no support in the specification that any portion from KGF that would possess preferential mitogenic activity of a KGF polypeptide and comprise "a sufficient number of amino acids 32-64 to confer on the polypeptide said preferential mitogenic activity".

Claims 45-46, 48-77, 81-82, 84-85 and 88 refer to polypeptides which stimulate BALB/MK cells to a greater degree compared to NIH/3T3 cells. However, the specification only provides for a polypeptide which stimulates BALB/MK cells 50 times greater than NIH/3T3 cells, rather than the varying degrees which are now recited in the claims (support is based on the previously filed claims). The instant specification does not provide for these new limitations of stimulation, nor does it provide for KGF polypeptides that differ in their ability to stimulate BALB/MK cells. A single KGF polypeptide is provided and it has the amino acid sequence as depicted in Figure 7, absent evidence to the contrary. Therefore, the claims are directed to subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, absent evidence to the contrary.

Claims 63-69 are directed to polypeptides of Figure 7 which are not supported in the instant specification as filed. It is not clear where the instant specification contemplates a KGF polypeptide which only comprises some number of amino acids 32-64 and amino acids 65-194, absent evidence to the contrary. There does not appear to basis in the instant specification as filed

for a polypeptide that contains some random selection of amino acids from amino acids 32-64 of Figure 7 fused to amino acids 65-194.

10. Claims 51 and 53-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Any claim which is not specifically recited below is indefinite for depending on an indefinite claim because the further limitations of the dependent claims do not correct the deficits indicated below.

Claim 51 is indefinite for the recitation of "selectively bind". The metes and bounds of this claim cannot be determined because it is not clear what is meant by "selectively". If this recitation means that the antibody binds to the polypeptide to the exclusion of all other proteins, then the claims are not enabled (see above). If this recitation means that the antibody binds to the polypeptide such that the antibody does not significantly react with other KGF polypeptides or does not significantly react with other polypeptides in general, the claims do not reflect this distinction.

Claim 53 is unclear and indefinite for the recitation "wherein the segment is a truncated polypeptide of Figure 7 which is N terminally truncated within the region of amino acids 32-78". It is not clear if the segment is the truncated portion or the portion of the polypeptide that remains after the truncation. For example, if the molecule was truncated at position 60, is the "segment"

amino acids 32-60 or 61-78 or 61-194. From the current recitation, the metes and bounds of the segment are not clear or definite.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April 1, 1999

Christine Saoud, Ph.D.
Christine Saoud
Patent Examiner
Art Unit 1646